Notice to Readers

Clinical Update: Impact of HIV Protease Inhibitors on the Treatment of HIV-Infected Tuberculosis Patients with Rifampin

In 1995 and 1996, the Food and Drug Administration (FDA) approved three products in the new protease inhibitor class of drugs—saquinavir (Invirase™), ritonavir (Norvir™), and indinavir (Crixivan™). Another drug in this class of agents, nelfinavir (Viracept™) (Agouron Pharmaceuticals), is expected to be available soon from the manufacturer through an expanded-access program. All four drugs, which inhibit HIV protease and thus interfere with viral maturation and replication, are the most potent antiretroviral agents available to treat patients with HIV disease (*1*). However, these protease inhibitors interact with rifamycin derivatives, such as rifampin and rifabutin, which are used to treat and prevent the mycobacterial infections commonly observed in HIV-infected patients. Rifamycins accelerate the metabolism of protease inhibitors (through induction of hepatic P450 cytochrome oxidases), resulting in subtherapeutic levels of the protease inhibitors. In addition, protease inhibitors retard the metabolism of rifamycins, resulting in increased serum levels of rifamycins and the likelihood of increased drug toxicity (*2*). This report describes approaches for managing patients who are candidates for or who are undergoing protease inhibitor therapy when tuberculosis (TB) is diagnosed and presents interim recommendations for managing these patients until additional data are available and formal guidelines are issued.

BACKGROUND

Rifampin is an essential component of the currently recommended regimen for treating TB (*3*). This regimen is efficacious in treating HIV-infected patients with TB and consists of isoniazid and rifampin for a minimum of 6 months, plus pyrazinamide and either ethambutol or streptomycin for the first 2 months (*4,5*). Therefore, the pharmacokinetic interactions between protease inhibitors and rifampin are important for health-care workers involved in TB control and the care of patients co-infected with TB and HIV because clinicians may decrease or restrict the use of rifampin in the treatment of patients who are candidates for therapy with both protease inhibitors and rifampin. Prompt initiation of appropriate drug therapy for patients with HIV infection who acquire TB is critical because TB may be rapidly fatal (*6*). Drug therapy is a critical personal health measure for curing TB and minimizes the impact of this disease on the progression of HIV infection; in addition, drug therapy is a major public health measure for interrupting the transmission of *Mycobacterium tuberculosis* to persons in the community.

Currently, the manufacturers' product labeling for protease inhibitors contraindicates, does not recommend, or discourages the concurrent administration of rifampin and protease inhibitors. Because of the common association of TB and HIV infection, an increasing number of patients probably will be considered candidates for rifampin and protease inhibitors. The management of these patients is complex, requires an individualized approach, and should be undertaken only by or in consultation with an expert. In addition, all HIV-infected patients at risk for TB infection should be carefully evaluated and administered isoniazid for preventive treatment if indicated, regardless of their status for being prescribed protease inhibitor therapy.

HIV Protease Inhibitors — Continued

MANAGEMENT OPTIONS

TB Management for Patients for Whom Protease Inhibitor Therapy Is Being Considered but Has Not Yet Been Initiated

For HIV-infected patients diagnosed with drug-susceptible TB and for whom protease inhibitor therapy is being considered but has not been initiated, the suggested management strategy is to complete TB treatment with a regimen containing rifampin before starting therapy with a protease inhibitor. The duration of this anti-TB regimen is at least 6 months, and therapy should be administered following current guidelines published by the American Thoracic Society and CDC (*3*), including the recommendation to carefully assess clinical and bacteriologic response in patients co-infected with HIV and to prolong treatment if response is slow or suboptimal. Antiretroviral agents other than protease inhibitors may be used concurrently with this regimen. Directly observed therapy (DOT) is routinely recommended for the treatment of TB to ensure adherence with the recommended regimen and is available through local health department TB-control programs. Among patients who adhere to therapy, four-drug regimens are expected to be effective even in those infected with strains of *M. tuberculosis* resistant to isoniazid or streptomycin alone. However, the management of patients with drug-resistant TB should be evaluated on a case-by-case basis and individualized based on the results of drug-susceptibility studies.

TB Management Options for Patients Undergoing Protease Inhibitor Therapy

There are three options for managing HIV-infected patients with TB who are undergoing protease inhibitor therapy when TB is diagnosed. One option is to discontinue therapy with the protease inhibitor while undergoing a TB treatment regimen that includes rifampin. However, because of the potential that interruptions in the administration of the prescribed protease inhibitor can induce HIV resistance to the protease inhibitor and possibly to other drugs within the protease inhibitor class (*1*) and because discontinuation of protease inhibitor therapy may be associated with a detrimental effect on the patient's clinical status, some clinicians may be reluctant to discontinue protease inhibitor therapy for the duration of TB treatment. In such cases, two additional options may be considered. Because the risks and benefits of all these options are unknown, clinicians should individualize management decisions on a case-by-case basis to provide optimal patient care.

Option I. This option involves discontinuing therapy with the protease inhibitor and completing a short (minimum 6 months) course of TB treatment with a regimen containing rifampin. This anti-TB regimen should be administered following current guidelines published by the American Thoracic Society and CDC (*3*), and the duration of therapy should be prolonged in patients with slow or suboptimal responses. Protease inhibitor therapy may be resumed when treatment with rifampin is discontinued. Antiretroviral agents other than protease inhibitors may be used concurrently with rifampin. Although the risks associated with a complete discontinuation of protease inhibitor therapy while undergoing TB treatment are unclear, they may be serious; however, the risks and complications associated with TB treatment regimens that do not include rifampin are known. Potential consequences include prolonged duration of therapy to at least 18–24 months, increased likelihood of treatment failure and mortality (*7,8*), slower conversion of sputum culture to negative with patients remaining infectious for longer periods of time, and the adverse effect of TB disease on the

HIV Protease Inhibitors — Continued

progression of HIV infection (*9,10*). Therefore, nonrifampin-containing regimens are not recommended for the treatment of rifampin-susceptible TB.

Option II. To minimize the interruption of protease inhibitor therapy, one option is to use a four-drug TB treatment regimen that includes rifampin (i.e., daily isoniazid, pyrazinamide, rifampin, and ethambutol or streptomycin) for a minimum of 2 months and until bacteriologic response is achieved (i.e., sputum conversion to culture-negative status), and the results from susceptibility testing are available. After bacteriologic response and drug susceptibility have been documented (usually 3 months), treatment may be modified to a 16-month continuation-phase regimen consisting of isoniazid (15 mg/kg) and ethambutol (50 mg/kg) two times per week. This regimen allows the reintroduction of protease inhibitor therapy. Some experts consulted for this report recommended adding a third drug, such as streptomycin, during this continuation phase if the infecting organism is not resistant to the drug. Option II cannot be recommended for patients with proven isoniazid-resistant TB.

Option III. The other management option is to continue protease inhibitor therapy with indinavir (800 mg every 8 hours) and administer a four-drug, 9-month TB-treatment regimen containing daily rifabutin (150 mg/day) instead of rifampin. When this option is used for TB management, clinicians should conduct careful monitoring, possibly including measuring serum concentrations of rifabutin—a service available only in specialized centers in the United States. This alternative TB therapy is recommended based on the pharmacokinetic characteristics of rifabutin and limited data from clinical trials. Rifabutin is a rifamycin derivative with comparable anti-TB activity in vitro but with less hepatic P450 cytochromic enzyme-inducing effect than rifampin (*11,12*). An international multicenter study indicated that a 6-month regimen containing rifabutin, at the daily dose of either 150 mg or 300 mg, was as effective for treating TB as a similar regimen containing rifampin (*13*). In a small clinical trial, a rifabutin-containing regimen was effective in treating TB in patients co-infected with HIV (*14*). In addition, limited data from pharmacokinetic studies suggest that the combination of rifabutin at 150 mg/day and indinavir resulted in acceptable levels of both drugs (*15*). Option III cannot be recommended for patients undergoing therapy with ritonavir or saquinavir. For these patients, the decision to change the prescribed protease inhibitor to indinavir and to prescribe rifabutin for TB therapy should be made in consultation with an expert in the use of protease inhibitors to manage HIV infection. In the United States, rifabutin is approved by FDA for the prevention of disease caused by *M. avium* complex (MAC) but not for the treatment or prevention of TB.

ADDITIONAL RECOMMENDATIONS

Neither option II nor option III have been studied in large clinical trials of HIV-infected patients or patients undergoing protease inhibitor therapy during TB treatment. For these reasons, if either of these options are selected for managing patients with TB, CDC recommends the following interim guidelines until additional data are available and formal guidelines are issued: 1) on initiation of therapy, perform frequent bacteriologic evaluations to document sputum conversion to culture-negative status, and after culture conversion, to detect any possible treatment failures, 2) extend the duration of therapy to at least 18 months for option II or 9 months for option III, 3) use only indinavir with option III, 4) carefully monitor for drug toxicity, 5) use DOT throughout, and 6) reevaluate periodically during the first 2 years after comple-

HIV Protease Inhibitors — Continued

tion of therapy (including an assessment of bacteriologic status at six months) and instruct patients to promptly report symptoms compatible with relapse of TB disease. The management of HIV-infected patients diagnosed with drug-resistant TB or diagnosed clinically with TB but without culture and susceptibility-testing results should be evaluated on a case-by-case basis and performed in consultation with a TB expert.

CONCLUSIONS

In the future, concurrent use of protease inhibitors with rifampin might be possible by modifying the doses of both to compensate for the drug interaction. For example, based on limited data submitted to FDA during the new drug application review for ritonavir, a slight increase in the dosage of ritonavir and a reduction by half in the dosage of rifampin may have resulted in satisfactory levels of both drugs. However, this option cannot be recommended until data from larger, more detailed studies are available and will require careful monitoring of the serum levels of rifampin.

Interactions between protease inhibitors and the rifamycins also have complicated prophylaxis and treatment for disseminated MAC disease. Rifabutin is one of the drugs recommended for MAC prophylaxis (*16*). According to the manufacturer of indinavir, rifabutin at half the dose (150 mg) can be used for MAC prophylaxis simultaneously with indinavir. Other options for MAC prophylaxis are clarithromycin and azithromycin (*17,18*), two macrolide antibiotics approved by FDA for this purpose and for which interactions with protease inhibitors are expected to be less of an issue. In November 1996, a joint working group of the Public Health Service and Infectious Disease Society of America will update recommendations for MAC prophylaxis.

To reduce the likelihood of drug interactions while providing optimal anti-TB care for HIV-infected persons, health-care workers involved in the care of patients with TB and health-care workers involved in HIV clinical care are encouraged to coordinate efforts and thus ensure the best possible outcome for these patients. CDC's Research and Evaluation Branch, Division of Tuberculosis Elimination, National Center for HIV, STD, and TB Prevention, (telephone [404) 639-8123]) requests the inclusion of clinical information in the comments section of TB surveillance reports from private practitioners or health department staff who manage HIV-infected patients undergoing protease inhibitor therapy when TB is diagnosed.

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HIV Protease Inhibitors — Continued

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